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Existence of Premunition in Natural or Experimental Rickettsiosis of the Dog.

by A. Donatien and F. Lestoquard.

Bull. Soc. Pathol. Exot., 29:378-383, 1936.

In the meeting of 12 June 1935 of the Société de Pathologie Exotique, we have noted the existence in Algeria of a pathogenic Rickettsia of the dog, which we have proposed to name Rickettsia canis. This parasite is very frequent in Algeria, since, in 212 examinations of blood film preparations of sick dogs effected since May 1935, it has been found 42 times, whereas Piroplasma canis was only discovered 10 times. We often happened to receive some previously deducted blood film preparations of dogs presenting hyperthermia and some general signs which one supposes are attacks of piroplasmosis because they were carriers of a large number, to a greater or lesser degree, of ticks of the species Rhipicephalus sanguineus. Very rarely is the piroplasma encountered: it is for this reason that, from 1926 to 1935, on 158 examinations of blood from sick dogs, Piroplasma canis has only been found 18 times. We have certainly let slip by, a more or less important number of cases of rickettsiosis in the other 140 previous deductions, for which we had concluded that the examination had given only a negative result.

Rickettsiosis is transmitted naturally by the tick Rhipicephalus sanguineus, which is infectious at every stage, and among which the virus is hereditary. This tick is, in Algeria, very frequent from April to October. It is called "the dog tick" because it has a marked predilection for this species. It is exceptionally encountered from the first of November to the following Spring.

Canine rickettsiosis is a serious disease, often fatal. It is characterized clinically by high and continued temperature, which drops suddenly at the approach of death. The principal sign consists of an extreme drowsiness, which often is a veritable torpor. The dog, indifferent to all that goes on around him, neither eats nor drinks and rapidly falls away. Most often one sees at the level of the abdomen on the inner surface of the thigh an exanthema of variable importance. The skin shows spots made up of effusions of blood in the derma and which are visible on the inner side of the integument, when this is lifted up.

Hyperthermia, nervous signs and the exanthema make it possible to classify this disease in the group of exanthematous fevers.

At the autopsy, one does not see any other lesion than a slight hypertrophy of the spleen whose pulp has remained solid, and a red and diffuent bone marrow.

The diagnosis is made on a living animal by finding, on a blood film preparation, a large number, to a greater or lesser degree, of Rickettsia in the monocytes. Often enough the parasite is very rare and a prolonged examination is necessary to show its presence. In an autopsy, on the contrary, the richness of certain organs is such that a rapid examination suffices to detect the Rickettsia. For the order of frequency of the parasite in the organs or tissues,

these can be classed as follows: very rich in the lungs and meningeal capillaries (which explains without doubt the somnolence), then the liver, then the kidney, then the hematopoietic organs: bone marrow, spleen and ganglia. Rickettsia are equally to be found in the adrenal glands, in the pancreas, in the heart muscle, in the intestinal mucosa, in the derma, notably at the level of the blemishes. The blood of the auxiliary vein is sometimes also abundantly parasitized: it is at this level that we saw R. canis for the first time.

The richness of the lung and of the liver makes it possible to have a certain and rapid diagnosis of a living animal by examining smear preparations of a fragment of these organs obtained by puncturing. The technique of puncturing the liver has been described by Ch. Nicolle and Conor. The puncture of the lung is done at the level of the middle part of the thorax by means of a needle 1.5 mm. in diameter and 5 cm. long. The needle mounted on a syringe is forced perpendicularly into the lung. One draws out finally to extract some blood and a bit of lung tissue which, crushed, serves to make the smears. The result is much more rapid than the examination of the peripheric blood circulation, which is often negative, whereas the examination of a lung smear shows the Rickettsia after some moments of searching.

This intense infection of the lung has led us to study whether the parasites persist in this organ after the clinical cure.

Our colleague Plantureux sacrifices each year a large number of pounded dogs either to prepare a serum against the disease at a young age, or to prepare a formalin anti-rabbies vaccine. We were thus able, from 6 November 1935 to 18 March 1936, to examine lung smears from 106 dogs. These are the results:

November 1935:	12 dogs examined,	1 presenting <u>Rickettsia</u> ;
December 1935:	26 dogs examined,	5 presenting <u>Rickettsia</u> ;
January 1936:	9 dogs examined,	2 presenting <u>Rickettsia</u> ;
February 1936:	46 dogs examined,	15 presenting <u>Rickettsia</u> ;
March 1936:	13 dogs examined,	4 presenting <u>Rickettsia</u> .

Admitting that the dogs were infected at the time when Rhip. sanguineus is abundant, that is in later October, it is evident that in February and March, some four and five months after the infection, the Rickettsia are still present in the organism. The conclusion then is that the evolution of Rickettsiosis of the dog takes in an acute attack with the first invasion, followed by a prolonged state (5 months or less) of chronic infection.

This idea of the persistence of the virus is verified in the course of the experimental study of the disease. By inoculation of blood or dilution of organs (lung) taken from a subject at the time of the acute attack, this (virus) can in fact be transmitted to a receptive species. Up to now, the receptive species are reduced to two: the dog and the Macacus inuus monkey.

One can experiment with two strains of the virus:

one from the annex of the Institut Pasteur d'Algerie located at Kouba (in the suburbs of Algiers);

the other from Boufarik and which has been sent to us by our associate Rampon by means of ticks collected in a kennel where the disease existed: 6 dogs

sick, 4 dead.

With the Zouba strain we have made the following experiments:

1. Dog 1 presented in the month of May 1935, an acute attack of the natural disease. In his blood, R. canis are found from 16 May to 4 June. After this date, the parasite is no longer shown and in a way parallel, a clinical cure is achieved. 11 July, a splenectomy is performed. On the smear of the spleen examined, one sees R. canis. Again after 15 July, the parasite is regularly observed by examining the blood. Simultaneously the temperature curve varies between 39 and 40 degrees, with a peak at 40.6 degrees on 27 July. The parasite disappears on 6 August. The animal dies on 27 August. R. canis are again found in the blood of the auxiliary vein and in the bone marrow.

Thus, 37 days after the clinical cure, the splenectomy has determined the reappearance of R. canis in the blood of the peripheral circulation.

2. 26 June 1935, the spleen is removed from monkey 22, which had presented an experimental attack from 7 to 14 June. The smears of the organ show the presence of R. canis. This spleen, crushed and emulsified, is inoculated in halves, into two monkeys 10 and 11. Monkey 10, ninth with the disease, presents, after 7 days of incubation, a typical attack. Monkey 11, cured 18 days previously of experimental rickettsiosis, does not present any reaction. This same monkey 11 whose initial infection dates back to 17 May 1935, progressively wastes away and finishes by being sacrificed in extremis on 9 November 1935. 60 cm³ of his blood are inoculated into monkey 14, which after 7 days presents a distinct attack of rickettsiosis.

Thus, 18 days after the clinical cure, monkey 11, has endured without damage a reinoculation. Furthermore, it has been possible to establish the presence of R. canis 156 days after the termination of the acute attack of the first invasion.

With the boufarik strain we have made 12 passages on 22 dogs by inoculation of blood or of dilution of organs removed at the time of the acute attack. In the course of this experimental study, the details of which will be published at the completion of the study, we have been able to obtain some results analogous to those which we acquired previously.

1. Dog 28, inoculated 20 September 1935, has presented after 8 days of incubation an acute attack of 16 days duration, followed by clinical cure. 16 November, this animal was splenectomized. Some R. canis were seen on the smears of the removed spleen. Furthermore, from 18 November to 7 December, R. canis has been regularly proved present in the microscopic examination of the blood. The temperature rose above 39 degrees on 27 and 28 November and on 2 and 3 December.

Then, 33 days after the clinical cure, R. canis remained in the organism of dog 28 and the splenectomy provoked a parasitic attack accompanied by a slight attack of fever.

2. We have been able to prove the resistance of 2 dogs cured of an acute attack of rickettsiosis.

Dog 36, of the 4th passage, inoculated on 23 October 1935, presented a fever and parasitic attack, which ended 18 November.

Dog 37, of the 5th passage, inoculated 23 October 1935, developed a fever, parasitic and clinical (marked drowsiness, exanthem) attack, which ended in cure on 13 December.

These two dogs were reinoculated on 26 December, with the 9th passage, at the same time as the new dogs 5 and 151.

Dog 5 began to react on 3 January 1936 and was sacrificed 8 January to furnish the virulent matter destined to assure the 10 passage.

Dog 151 likewise began his reaction of 3 January in presenting a fever, parasitic and clinical attack ending in death on 31 January.

Dogs 36 and 37, however, have presented neither fever nor parasitic attack.

Thus 38 and 23 days after the cure of the acute attack, dogs 36 and 37 have endured, without reaction of any sort, a reinoculation of R. canis.

~~From these~~ observations and experiments, ~~it results~~ that:

1. R. canis remains in the organism a long while (5 months or less) after the clinical cure of an acute attack (natural or experimental);
2. Animals cured of an acute attack endure a reinoculation without presenting any morbid symptoms.

The objection might arise that among the 22 dogs that we have inoculated to assure the 12 passages of R. canis of the Boufarik strain, a certain number could have been in a state of chronic infection. However, upon inoculation, all have presented an acute attack of greater or lesser severity. We might answer that these animals received considerable doses of virus (at least, by intravenous inoculation 20 cm³ of blood in which R. canis was proven present by microscopic examination). It is known that the immunity, and so much the more, the premonition can be broken when the test is very strong. Finally the gravity of the attack varied and it is possible to think that the animals which reacted slightly were chronically infected with R. canis.

3. Splenectomy of an animal cured more than one month previously is followed by a fever and parasitic attack. This is what one finds in certain parasitic diseases: piroplasmosis, anaplasmosis, bartonellosis, diseases which confer a premonition.

These diverse classes of facts show clearly that rickettsiosis confers premonition and not immunity.

Further, this long persistence of the virus in exanthematous fevers due to these Rickettsia has already been shown to exist many times. We cite, among others, the first case and the two latest.

1. In 1921, Bacot picked up at Warsaw, between 31 March and 5 April, some lice infected with extra-cellular Rickettsia. He presented, after 7 April, a

feverish acute onset, followed by a pathological state analogous to trench fever. During this same period, Bacot nourished on himself a stock of lice obtained from England and whose line was undamaged by rickettsia for more than two years. This absence of infection was again verified just before the beginning of Bacot's sickness. On 27 April, Rickettsia began to appear on the lice obtained from England and their study showed that they were all extra-cellular. Finally Bacot continued to infect the lice up to the month of September, which was 4 months after the beginning of the sickness and 3 months after complete cure. There is every reason to think that Bacot had been infected by the lice from Warsaw and that the Rickettsia which he had transmitted to the new lice from London was identical to those which infected naturally the Polish lice (1).

2. We presented at the meeting of 24 December 1935 of the Academie de Medecine a short article in which we demonstrated the persistence of R. canis in the organism after cure. Our conclusion was as follows: "The existence of premunition in one disease of the group of exanthematous fevers leads us to wonder if other infections of man and animals (Heartwater), caused by Rickettsia, do not admit of premunition. If this is the case, the persistence of the virus among the clinically cured subjects highlights certain points still obscure in the epidemiology of these diseases (2)."

3. At the meeting of 8 January 1936 of the Société de Pathologie Exotique, Lepine and Sautter showed that the virus of mouse typhus can be recovered in the brain of a spermophile (burrowing rodent) up to the 374th day after the inoculation, and their concluding words are analogous to our own: "the reported facts are classed among the longest persistences known of virus in the neuraxis and can be used to aid in the explanation of certain points still obscure in the epidemiology of typhus." (3)

All these facts speak in favor of the persistence of the virus and correlatively, of the existence of premunition in the exanthematous fevers due to these Rickettsia.

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Footnotes

(1) Wolback, Todd, and Palfrey. The Etiology and Pathology of Typhus, 1922, pp. 130-131.

(2) A. Donatien and F. Lestoquard. "Sur la Persistance de R. canis dans l'Organisme du Chien après guérison," Bull. Acad. Méd., v. 114, 1935, p. 857.

(3) Lepine and Sautter. "Sur la durée de la Conservation du Typhus Murin dans l'Encephale du Spermophile," Bull. Soc. Path. Exot., v. 29, 1935, p. 13.